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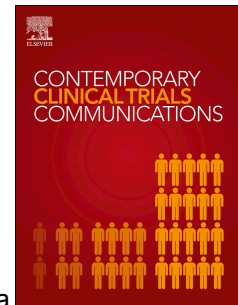
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Mediterranean diet based intervention in pregnancy to improve maternal and fetal outcomes: Methodological challenges and lessons learned from the multicentre ESTEEM study

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Abstract:

Introduction: Evaluating complex dietary interventions such as Mediterranean diet in pregnancy presents unique methodological challenges. We present the challenges and the lessons learned from a multicentre randomised trial (ESTEEM) on Mediterranean-based dietary intervention in pregnancy.

Methods: We recruited pregnant women who met our predefined inclusion criteria and randomised those with metabolic risk factors to the Mediterranean-based dietary intervention or routine antenatal care. We evaluated the effect of the ESTEEM intervention on composite maternal and fetal outcomes.

Challenges and solutions: The main challenges were encountered in recruiting to ESTEEM, delivering the intervention, engaging clinical staff, assessing adherence and choosing the outcome measures. The large sample size coupled with the slow recruitment rate forced us to extend the recruitment period by 4 months. The limitation in available resources was overcome by opening sites in a step-wise approach. Engaging healthcare providers was promoted by embedding the recruitment and the follow-up activities into current clinical practice, and promoting research skills training. We delivered the intervention early on in the pregnancy to promote the dietary effect on healthy placentation and reduce metabolic risk factors. Participants and their families were actively involved in the dietary intervention to improve adherence through a series of group teaching sessions. A user-friendly short dietary questionnaire was developed and validated to assess adherence to the intervention. The trial composite primary outcome was chosen in consensus based on input from a panel of experts.

Conclusion: The ESTEEM experience offers an insight into future pragmatic nutritional studies in pregnancy.

Introduction:

Women with metabolic risk factors such as high BMI, dyslipidaemia and chronic hypertension are at increased risk of developing adverse outcomes such as gestational diabetes, pre-eclampsia and admissions to neonatal intensive care units.(1) With the rapidly increasing number of women entering pregnancy as obese or overweight, researchers are more focused on evaluating the role of dietary and lifestyle interventions to improve maternal and fetal health outcomes.(2)

Mediterranean based diet has been shown to improve cardiovascular outcomes in a non-pregnant population.(3,4) The effect of such diet on pregnancy outcomes in women with metabolic risk factors is not known.(5,6) Evaluating complex dietary interventions such as those based on Mediterranean diet in a pregnant population poses unique methodological and conceptual challenges.(7,8) The lack of standardised, and accepted methods to evaluate the effectiveness of dietary interventions may lead to inconsistent findings in nutritional epidemiology. Factors such as participants' adherence to the intervention and the accuracy of the dietary assessment methods could also affect the study findings.(9)

We undertook a multicentre randomised trial (ESTEEM) to assess the effectiveness of a Mediterranean based diet intervention to reduce complications in pregnant women with metabolic risk factors. In this article we highlight the methodological challenges and the lessons learned from the ESTEEM study.

Methods:*Study design*

ESTEEM is a randomised trial embedded in a cohort study. Recruitment started in September 2014 and finished in February 2016 in five tertiary maternity units in the UK (covering 30,000 deliveries per year). We included pregnant women who met the following criteria: at least 16 years of age, BMI between 18.5 Kg/m² and 40 Kg/m², singleton pregnancy of 18 weeks gestation or less, good understanding of written and spoken English, able to consume nuts and olive oil and follow a Mediterranean diet lifestyle. We randomised eligible women with metabolic risk factors (raised serum triglycerides (≥ 1.7 mmol/L), obesity (BMI ≥ 30 Kg/m²), or chronic hypertension (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic blood pressure)) to the ESTEEM dietary intervention or routine antenatal dietary care. Participants with no metabolic risk factors were followed up in the cohort group and only outcome data were collected (Figure 1). The primary outcome is a composite maternal outcome defined as pre-eclampsia (new onset or superimposed) or gestational diabetes; and a fetal composite outcome defined as stillbirth, small for gestational age fetus (birth weight less than 10th centile) or admission to the neonatal intensive care unit. The full protocol of the ESTEEM study has been reported previously (10).

The ESTEEM dietary intervention is based on Mediterranean diet lifestyle with education to modify lifestyle choices. The key components of the diet included high intake of fruit and vegetables, non-refined grains, legumes; moderate to high consumption of fish; small to moderate intake of poultry and dairy products such as yoghurt and cheese; low consumption of red meat and processed meat and avoidance of sugary drinks, fast food and food rich in animal fat. In particular, ESTEEM promoted high intake of nuts (including walnuts, hazelnuts, and almonds estimated at 30 g/day) and high intake of extra virgin olive oil as the main source of fat (estimated at 0.5 L/week). The intervention also included dietary education

sessions, grocery shopping advice, cooking recipes for a healthy diet and advice for appropriate meal choices at restaurants.

Randomised participants were also consented to collect umbilical cord samples after delivery to be used for future research on the effect of the dietary intervention on fetal biochemical outcomes.

We expected the ESTEEM dietary intervention to reduce the incidence of the composite primary outcome by 30%, assuming a 24% background risk in our population. Allowing for a 20% dropout, the sample size required is 1230 eligible women to ensure an 80% power at the 5% significance level for maternal and fetal composite outcomes. ESTEEM has completed its recruitment and currently in the follow up phase.

Challenges and solutions

Recruitment

The initially planned recruitment period was 14 months. However, this was proven to be insufficient after the pilot phase given the large sample size required and the slower than expected recruitment rate. After discussion with the trial steering committee (TSC) we resolved to extend the recruitment period by further four months, and increased the number of recruitment centres from three to five major tertiary maternity units in the UK (4 in London and 1 in Birmingham). We opened sites in a step wise approach, which enabled us to test and troubleshoot recruitment challenges at each site prior to opening another site. This allowed us to allocate the trial resources judiciously and to factor in the relatively long

intervention and follow up periods for each participant.(11) The recruitment centres were closed in a similar fashion based on a forecast of recruitment figures and staff allocation.

We implemented a series of evidence-based measures designed to embed the trial recruitment and follow-up process into clinical practice at the ESTEEM sites.(12) We provided research training to clinical midwives in groups and individually with the objective to enable them to recruit and consent participants alongside routine antenatal care. Clinical staff engagement in ESTEEM was promoted with a series of talks and interactive teaching sessions on the benefits of involving patients in research studies. We recognised the contribution of our top recruiting midwives at each of the sites with acknowledgment certificates, dissemination in newsletters and research meetings, and awarded small financial incentives. We attached an additional ESTEEM eligibility sheet to all booking clinical notes to remind clinical staff to recruit booking women. A team of dedicated research staff provided daily support in the antenatal clinics to help screen and recruit women at their booking visit. Participants who required additional time to consider the trial before consenting were followed up with telephone calls by our team. Overall clinical midwives consented a third of participants recruited into ESTEEM.

Intervention

In ESTEEM, we focused on delivering the intervention early in the pregnancy to promote the dietary effect on healthy placentation and reduce metabolic risk factors. We initially planned to deliver the intervention by 18 weeks gestation. However, this was not always possible, as many participants were not able to attend their initial appointment. Taking a pragmatic approach, and reflecting on clinical practice, following our pilot phase we decided to extend

the intervention window till 20 weeks gestation. This ensured that participants who were attending for their 20 weeks detailed ultrasound scan were involved in the intervention delivery process.

Engagement

Participants' beliefs and food culture are major confounders in such trials particularly in pregnant women.(13) Engaging participants in the planning of the intervention is advised to ensure higher adherence to the intervention.(14) Traditionally, women are advised to "eat for two" and the health benefits of certain food groups are overrated.(15) Mothers are also more likely to follow advice from peers, partners and family members compared to health care professionals.(16) We actively involved our participants in the design and the implementation of the required dietary changes. Dietary interventions based on the social cognitive theory have been shown to be effective to improve compliance.(17) Building on this, we delivered a number of educational sessions to boost the participants' knowledge on nutrition in pregnancy on topics such portion sizes and the benefits of Mediterranean diet to both mother and baby. We also prompted participants to share experiences and success stories with each other to improve adherence to the intervention. Additionally, we involved partners and the whole family where possible to improve adherence particularly in larger families where pregnant women may not do the shopping and the cooking for the entire household. We encouraged participants to set personalised goals based on the SMART model (specific, measurable, achievable, relevant and time specific) to create a personalised working plan and implement the recommended dietary changes in their lifestyle.

purchasing extra virgin olive oil and nuts may be too expensive to some of our participants in the intervention group, which could affect adherence.(18) We tackled this by providing regular supply of extra virgin olive oil to cook for the whole family, and sachets of nuts (walnuts, hazelnuts, and almonds) for personal use throughout the pregnancy.

We planned the following two intervention sessions (at 20 and 28 weeks) in a group setting for both the participants and their partners. The aim of these sessions was to provide further knowledge on the benefits of Mediterranean diet, healthy shopping habits, reading food labels and beneficial food for the baby. The sessions also aimed to support the participants by exploring obstacles arising and sharing experiences.(16) Planning these sessions was not always possible in a group setting and often took place with only one or two participants. For those participants who missed a session or two we attempted to reschedule or arranged to send them the nuts and extra virgin olive oil by post to ensure they maintain their intake and compliance with the intervention.

Assessing adherence to dietary intervention

Accurate estimation of participants' basal dietary intake was required before introducing the intervention.(7) We therefore used the multi-pass 24 hour dietary recall technique combined with a series of focused questions to carefully assess the participant's dietary habits at baseline.(19) This helped our dieticians to identify areas for improvement and the necessary changes towards adopting a Mediterranean based diet.

Our population consisted mainly of multiparous women, often from a transiently immigrant background. Many of our participants had low literacy of English language, and had difficulties to complete a complex tool such as weighted food diaries.⁽²⁰⁾ Using such a labour intensive tool was particularly not ideal for the majority of our participants looking after large families and in full time employment.⁽⁸⁾ Since our main objective was to primarily quantify the participants' adherence to the planned intervention we decided to use a short 12 items food questionnaire focused that captured the main elements of a Mediterranean diet (The ESTEEM Q).

We adapted the ESTEEM Q from a similar questionnaire that was validated in a Mediterranean non-pregnant population.⁽²¹⁾ We amended the our questionnaire by removing two questions that were not applicable to our population (alcohol intake and sofrito, a tomato sauce made of a combination of tomato, olive oil, garlic, and onion) consumption) and added 7 dichotomous questions to investigate conditions specific to pregnancy that could affect the participants' dietary intake. We used a point scoring scale to assess adherence to the Mediterranean diet based intervention using previously validated cut-off values. ⁽²²⁾

We intended to use the number of retained empty packets of nuts and extra virgin olive oil as a marker of participants' consumption. However, we aborted the use of this method due to poor returns. The use of specific biomarkers such as alpha-linolenic acids for nuts intake and hydroxytyrosol for olive oil was another possibility to objectively assess nutrients' intake.⁽²³⁾ Using biomarkers has a number of limitations; they are expensive, invasive and provide only a snap shot view of the dietary consumption.⁽²³⁾ Taking into account the extra cost required, we opted to drop the use of biomarkers.

Given the above limitations we decided to assess the adherence to the intervention by evaluating the number of attended intervention sessions and comparing the scores obtained from the ESTEEM Q.

Control group

Selecting appropriate control subjects in dietary trials is often challenging in clinical settings (24). There is no clear guideline on what constitute a suitable control population for interventional dietary studies in pregnancy. In line with ESTEEM's pragmatic design, we decided to not impose any dietary requirement on our control group and provided usual antenatal care as per the national guidelines within the national health service. (25)

The pragmatic design of ESTEEM provides higher external validity to assess the effectiveness of the dietary intervention. Our population has diverse ethnic backgrounds with different food cultures, some of whom might be adopting a Mediterranean lifestyle already. Many participants were from transiently immigrant families with likely varying food habits. This could affect the validity of comparing dietary outcomes between the two groups

Assessment of outcomes

ESTEEM was designed as a pragmatic trial to assess the effectiveness of dietary intervention on composite maternal and fetal outcomes in clinical practice. We used a robust method to identify the components of the composite outcome based on a multi-stage modified Delphi survey of clinical and academic experts in obesity research in pregnancy.(26) Both pre-eclampsia and gestational diabetes were prioritised to be the most clinically important

maternal outcomes and were included in the composite primary outcome. Our panel of experts identified stillbirth, small for gestational age fetus (birth weight less than 10th centile) and admission to the neonatal intensive care unit to be the most clinically important fetal/neonatal outcomes and were incorporated into the composite outcome. We also decided to report on each of these outcomes individually as secondary outcomes. Reporting on dietary outcomes was restricted to the information collected in the ESTEEM Q.

Complete outcome collection after delivery was logistically challenging within the allocated time window. We dedicate a research midwife to screen the labour and postnatal wards daily for any ESTEEM patients in order to capture all new deliveries. We also crosschecked daily hospital admission records against our electronic records of the participants estimated delivery date to reduce loss to follow ups.

Collecting cord blood samples proved to be very demanding in terms of time and resources. We sought help from clinical midwives on the delivery suite to assist in collecting and reserving cord blood samples as per the ESTEEM protocol. We produced special ESTEEM stickers on the participants' maternity notes and wall posters on delivery suit to remind our midwives to collect the cord blood samples for eligible participants.(27)

Table (1) provides a summary of encountered challenges and applied solutions in ESTEEM.

Discussion

The notion that pregnancy could offer a unique window of opportunity to invoke change in mothers' lifestyle has inspired many researchers in recent years. However, to date, the

recorded success remains limited.(5) This is often attributed to the poor quality of available evidence and small sample sizes. Methodological deficiencies affect the effect size and the transferability of trial findings into clinical practice. Elements such as the timing of introducing the intervention in pregnancy, choice of population, compliance and dietary assessment methods are all important factors to consider when designing diet based interventional studies.(8)

The ESTEEM study was focused on evaluating the effectiveness of increased maternal intake of unsaturated fatty acids early in reducing metabolic disorders in pregnancy namely gestational diabetes and preeclampsia. The knowledge about the fatty acid disposition in pregnancy and role of the placenta in the metabolic changes is still somewhat limited.(28) Our theory is that a high intake of poly unsaturated fatty acids and mono unsaturated fatty acids will improve the endothelial function, reduce oxidative stress and reduce insulin resistance thus reducing metabolic risk factors. Obese mothers tend to develop higher concentration of plasma lipids such as triglycerides and very low-density lipoprotein throughout pregnancy. However, the levels of unsaturated fatty acids remain stable at pre-pregnancy levels.(29) Altering the maternal diet could help to increase the levels of these useful nutrients and amplify their role in reducing oxidative stress.(30) The design of the ESTEEM study will provide pragmatic evidence on the role of Mediterranean diet in improving pregnancy outcomes in clinical practice.

To date, our knowledge on the potential long term benefits of dietary intervention in pregnancy remains limited, in contrast to the proven adverse effect of obesity on long term maternal and childhood outcomes.(31,32) Nutritional studies should aim to engage

randomised postpartum cohorts in long term follow-up studies to evaluate long term health outcomes and retention of the intervention after pregnancy.

The maintenance of the intervention in the population and the prevalence of healthy lifestyle after the trial lifetime are also poorly investigated (5); often due to funding and resources limitations. Advances in dietetics' technology could help to address this challenge in future studies at low cost. The use of mobile apps and internet based interventions has been reported to be helpful in maintaining diabetic control and other chronic diseases.(33,34) Such methods could significantly help to gather more individualised and long term health outcomes.

Exploring the qualitative aspect in interventional trials is an important aspect to better develop and implement lifestyle interventions is. Qualitative research can help to gather more information on mothers views and attitude towards changing their lifestyle before, during and after pregnancy.(35) This is particularly helpful to explore potential obstacles to changing dietary habits in certain subgroups such as participants of low socio-economic status.(36)

Our knowledge about dietary interventions around pregnancy has evolved markedly in the last few years. However, several methodological challenges still persist. Innovative and creative research methods are needed to address this important public health issue.

Conclusion:

Dietary lifestyle interventions in pregnancy are associated with a number of methodological challenges. The ESTEEM experience offers an insight into future pragmatic nutritional studies in pregnancy.

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Conflict of Interest:

All authors disclose no conflict of interest.

Authors' contribution:

BHA wrote the first manuscript draft and is helping with in the study conduct, JD, SH and AP are co-ordinating the study conduct and drafted the protocol, EP is delivering the intervention, RH and LE designed the statistical analysis plan, TR, MBR, GH and KSK helped in developing the protocol, ST is the chief investigator for ESTEEM and overseeing the study conduct. All authors provided critical input to the manuscript.

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Table (1): Summary of challenges and solutions proposed in the ESTEEM study.

Domain	Challenge	Solution
Recruitment	Large sample size and slow recruitment rate	Extended recruitment by 4 months and opened more recruitment centres.
		Engaged clinical staff in the recruitment and follow up process
		Assigned dedicated research staff to screen antenatal clinics daily
Delivery of the intervention	Poor attendance to initial intervention sessions	Extended the intervention window up to 20 weeks gestation
Participants engagement with the study	Various food cultures and dietary habits among participants	Tailored intervention based on individual food habits assessment
	Improve adherence to the intervention	Actively engaged participants and their families in planning the required dietary changes to comply with the intervention
		Provided group dietary educational sessions
Adherence to the intervention	Assessing basal dietary intake	Used of a multi-pass 24 hour dietary recall with focused questions
	Choice of dietary assessment tool	Developed and validated a user friendly short dietary questionnaire specific to Mediterranean diet
Control group	Choice of control participants	Adopted a pragmatic approach with no specific dietary requirement in the control group
Outcomes	Choice of primary outcome	Developed a composite outcome of maternal and fetal outcomes prioritised by a panel of experts.
	Complete outcome collection	Assigned dedicated research staff to screen postnatal and labour ward and crosscheck participants against electronic records

Figure (1): ESTEEM study design including the screening, recruitment and randomisation process.

